

prior art references. By this amendment, the applicant has amended those claims to further define the invention over the prior art of record. Based on these changes, and the arguments presented here, the Examiner is requested to consider the merits of this patent application once again by way of advisory review before the necessity for an appeal of the rejection of this patent application.

The single ground for rejection to the claims of the applicant set forth by the Examiner was based on alleged obviousness under §103 over the reference to DeBlock taken with the papers to Zutra and Rangan. None of these papers discloses the creation of whole transgenic cotton plants as claimed by the applicant here. Viewed most expansively, these references merely individually suggest particular steps similar to some in the applicant's process claims. No single reference, and no combination of the cited references, enables the reproducible and reliable creation of transgenic cotton plants, as the applicant has done.

DeBlock teaches the use of *Agrobacterium* Ti plasmids as vectors for the genetic engineering of tobacco plants. DeBlock does also disclose the use of antibiotic resistance markers as a selection mechanism for transgenic plants cells. As noted by the Examiner, the Zutra paper does report the susceptibility of cotton to *Agrobacterium* infection. Also as noted by the Examiner, the paper to Rangan et al does teach the regeneration of non-transformed cotton plants from somatic embryos in culture. The Examiner argues that it would have been obvious to one of ordinary skill in the art to utilize the gene transfer method of DeBlock with cotton as a host, suggested by Zutra, and to combine those teachings with the concept of cotton somatic embryogenesis as taught by Rangan. The applicant respectfully disagrees.

The first problem lies with exactly what is taught about plant transformation by the paper to DeBlock. This paper teaches that the co-cultivation of *Agrobacterium tumefaciens* cultures with plant protoplasts.. The "protoplast-derived cells" (p. 1692) were then plated onto a solid medium containing the antibiotic which is to be the selection tool. This transformation of unorganized, individual plant cells lacking cells walls in co-culture with bacteria is quite a bit different from the transformation of excised differentiated tissue, such as the hypocotyl segments taught by the applicant here. For a teaching to be prior art sufficient to support an

obviousness rejection, the reference should clearly suggest to one of ordinary skill in the art that the subject procedure would actually work. Nothing in the reference to DeBlock provides any reason to believe that the *Agrobacterium* transformation of a hypocotyl segment of any species, no less cotton, would be successful. It is submitted, therefor, that the combination of references cited by the Examiner does not even make a case of *prima facie* obviousness, since not only is there no suggestion in the references how they may be combined, when combined they still do not suggest important features of the applicant's invention or its success.

While the undersigned suspects that the Examiner has grown tired of the argument, the fact remains that the Examiner's rejection is another variant of the "obvious to try" rejection. The combination of references suggested by the Examiner do not predict with any confidence the success of the process actually made to work by the applicant. At very best, these references suggest one of the many possible avenues of approach to try to achieve the desirable result, i.e. the transgenic cotton plant. They do not provide enough guidance to form a reasonable expectation that the process as utilized by the inventor here would actually succeed. Where the prior art gives only general guidance as to the particular form of the invention or how to achieve it, as here, obviousness may not be found. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1986).

The question of obviousness is to be considered in a particular time context. That time context is at the time of the making of the invention. Consider the fact that prior to the announcement by the applicant here, and the publication of the results of the research of he and his colleagues, no one had reported the successful production of a genetically engineered cotton plant. Submitted herewith is a copy of a story that appeared in the Dec. 5, 1986, Wall Street Journal. The applicants have previously submitted a copy of the paper publishing their results, Bio/Technology, 5:263-266 (1987), but a extra copy is submitted herewith for the Examiner's convenience. Both these publications, both reputable, cited the work of the inventor here as the first report of transgenic cotton plant. It should go without saying that cotton represents one of the major field crops in the United States, along with corn, soybean, and wheat. Yet at the time of the applicant's invention, there was not another single reported genetically

engineered cotton plant. As far as the undersigned and the applicant can determine, the applicant was the first to accomplish this objective.

If indeed the applicant was the first, that, of course only absolutely demonstrates novelty, not non-obviousness. But here, in this technology, and with this plant, it is submitted that this is compelling evidence of non-obviousness as well. The reason is the simple one that the genetic engineering of cotton was an objective sought by many. Note that the referenced Adang published application, assigned to Agrigenetics, suggested the use of a Ti plasmid vector to transform cotton with the gene for the *Bacillus thuringiensis* delta-endotoxin. Yet Adang's co-workers were not able to report an actually transformed cotton plant until Firoozabady et al published their paper in the fall of 1987. That publication was over four years after the original filing date of the Adang patent application. Thus is should be clear from the record before the Examiner that the objective was a sought-after one. And the applicant was the first to reach it. This, in itself, is compelling evidence of non-obviousness, sufficient to overcome a *prima facie* case of obviousness, even if one had been made.

The Examiner is knowledgeable enough in this technology to be aware that developing reproducible methods for the genetic engineering of new crop species is not easy. Not only must transformation and regeneration techniques be worked out, they must be complimentary. In other words, the transformation process must be capable of transforming a tissue that can be regenerated. In addition, a selection routine that permits efficient selection of transformed tissues, without significant spontaneous generation of resistant non-transformed tissues, must function. Note that the applicant did not use, and does not claim, a routine of coculture with protoplast as taught by DeBlock for use with tobacco. The fact is that, at the time of the applicant's invention, no technique was known to regenerate whole cotton plants from protoplasts. No one had demonstrated the effectiveness of a selection agent in transformed and regenerating tissues. There was also no certainty that the applicant's technique of transforming hypocotyl segments would give rise to transformed cultures when somatic embryos were induced in culture. Since no one had tried this multiple-step technique before, and since others were simultaneously unsuccessful in pursuit of the same difficult objective,

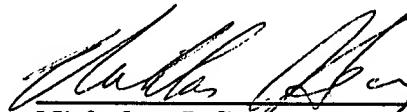
it would seem that only the application of hindsight could find the impressive achievement of the inventor here to be an obvious one.

The development of the ability to apply recombinant technology to plants has led many observers to predict a revolutionary change in the character of agriculture over the coming decades. For this potential to come even close to realization, the basic techniques must be developed to transform the commercially important crop plants. As experience has proven, there must be variations in techniques from plant to plant. The applicant here has invented the first reliable and reproducible procedure to make transgenic cotton plants. This is a step, and a significant one, in the realization of the potential of biotechnology in agriculture. It was not easy. If it was, the applicant and others would have done it sooner. It was not obvious either.

In view of the foregoing, the applicant respectfully asks the Examiner to once more review the merits of this application and its claims. The courtesy of an advisory action is solicited.

A separate petition for extension of time is enclosed for three months, both to make this amendment timely filed and to give the Examiner an opportunity to consider an advisory action before the necessity of an appeal.

Respectfully submitted,



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